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Award Number: W81XWH-07-1-0454

TITLE: Photonic Breast Tomography and Tumor Aggressiveness Assessment

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New York, NY 10019-2925

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
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14. ABSTRACT
The tasks performed and the progresses made during the current reporting period include: (a) pursuing planned training objectives of the researchers from the City College of New York (CCNY) through attending courses and seminars at the memorial Sloan Kettering Cancer Center (MSKCC); and (b) conducting research on development of non-invasive optical imaging and spectroscopic approaches for breast tumor detection. The CCNY researchers took five courses in the areas of cancer biology, biochemistry, genetics, and pharmacology and attended a molecular imaging seminar series and journal clubs to develop sound background in the biological and clinical aspects of cancer research. The research component involved application and further refinement of optical tomographic imaging using independent component analysis (OPTICA) for locating and cross-section imaging of a tumor in a model cancerous breast assembled using ex vivo breast tissue specimens. The OPTICA approach was able to detect, provide the location with an accuracy of ~ 1 mm and cross section of the tumor in the model cancerous breast.

15. SUBJECT TERMS
Breast cancer, near-infrared imaging, optical tomography using independent component analysis (OPTICA), training, molecular imaging, cancer biology

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4. INTRODUCTION

The HBCU/MI Partnership Training Award project, " *Photonic Breast Tomography and Tumor Aggressiveness Assessment*," is designed to establish a breast cancer training and research program at the City College of New York (CCNY) through close collaboration with the researchers at the Memorial Sloan Kettering Cancer Center (MSKCC). The focus of the training component of the project is to introduce the CCNY researchers who happen to be physical scientists and engineers to cancer biology and technology of modern breast cancer research. The objectives of the research component of the project are to develop optical imaging and spectroscopic approaches to (a) distinguish between aggressive and slow growing, metastatic and non-metastatic tumors, (b) non-invasively detect and diagnose breast tumors at early stages of growth.

While the emphasis of the program is on the training component during the first two years, significant progress has been made in both training and research during the first reporting period (June 15, 2007 – June 14, 2008) covered by this report.

5. BODY

The tasks performed and the progresses made during the current reporting period are as follows:

- Accomplishment of planned training objectives through attending courses and seminars at MSKCC; and
- Pursuing research on development of non-invasive optical imaging and spectroscopic approaches for breast tumor detection.

We provide a brief outline of our accomplishments in these areas, and refer to appended materials for detailed description where applicable.

5.1. Accomplishment of Training Objectives

The CCNY team of trainees included a graduate student, two postdoctoral research associates and a faculty member. The Year1 training emphasized familiarizing the CCNY researchers with the biological aspects of cancer research through attending relevant courses (*Specific Aim 0, Task 1*), as well as, seminars, lectures, and workshops (*Specific Aim 0, Task 5*). The specialized training strategy included: access to MSKCC resources; taking core courses in cell biology, biochemistry, genetics and pharmacology offered by the tri-institution consortium that includes MSKCC, the Rockefeller University, and Weill Cornell Medical College; and attending research seminars, journal clubs and clinical conferences.

Resources

All trainees have been granted MSKCC ID that provides them access to the libraries of the Hospital for Special Surgery, Rockefeller University and Weill Cornell Medical College. The trainees are on the mailing list for research seminar series and workshops.

Courses

The purpose of coursework is to prepare the trainees, who have a research background in physics and engineering with solid knowledge in biology, biochemistry, genetics, and pharmacological aspects of breast cancer research. Five courses were specifically selected from core courses in Biochemistry & Structural Biology, Cell Biology & Genetics, and Molecular

Biology (BCMB) programs and Pharmacology program in graduate education at tri-institution consortium. The courses attended are briefly outlined below and further details on the content are presented in *Appendix 1*.

Biochemistry: This is a two-quarter course in structural biology and contemporary biochemistry.

Molecular Genetics: This is a two-quarter course organized around the principles of genetic analysis, with examples chosen from organisms that best illustrate those principles.

Cell Biology and Development: This two-quarter course explored key aspects of cell and developmental biology at the molecular level.

Principles of Pharmacology: This one-quarter course was organized in three modules: general pharmacological principles, nervous and circulatory systems, and the remainder of the circulatory system along with host defense and endocrine systems.

Molecular Pharmacology of Cancer: This one-quarter course focused on the principles and applications of modern cancer therapeutic approaches.

Clinical Case Conferences and Journal Clubs

The trainees were assigned to attend the weekly early morning clinical conferences and journal clubs. The objective of participation in the clinical conferences is to teach the trainees clinical aspect of breast cancer care, which is important for developing a better understanding of the basic cancer research issues. The role of journal club is to expose the trainees to the cutting-edge research, and inculcate in them the abilities to carefully select and critically read the high-quality breast cancer research articles. The clinical conferences and journal clubs attended are as follows.

Breast Service (Surgery) Conference & Journal Club: The Breast Service Conference is held at MSKCC every Tuesday morning from 7:00 - 8:00 A.M. A Journal Club for surgical trainees follows the conference. At the conference, the multidisciplinary team consisting of breast surgeons, radiologists, pathologists, and oncologists discuss treatment for their recent cases.

Breast Cancer Medicine Service Conference and Journal Club: This conference is held on every Thursday morning from 7:30 - 8:30 A.M. followed by a Journal Club. This conference is a combination of administrative, patient care, and research planning and review.

Molecular Imaging Lectures and Journal Clubs

The trainees attended a didactic *molecular imaging lecture series* and *molecular imaging journal club*. An existing molecular imaging training grant to MSKCC from the Cancer Education and Career Development Program (R25T) of the National Cancer Institute (NCI) supports the lecture series and the journal club. The lecture series is held weekly from 5:00 - 6:00 PM on Tuesday. It is intended as an introductory overview of the major methodologies used for experimental molecular cancer imaging, illustrated with specific examples of phenotypic and genotypic imaging. Examples are drawn from nuclear, MRI/MRS and optical imaging methodologies. The organizers agreed to accommodate CCNY trainees in this lecture series.

Other Activities

The CCNY and MSKCC groups met regularly to discuss the progress during the Year 1 training. The CCNY researchers attended the *Era of Hope Meeting,* June 25-28, 2008 held in Baltimore, MD.

5.2. Development of Near-Infrared Optical Imaging Modality for Breast Cancer Detection

The research planned to be pursued in the project has two components: (a) development of non-invasive near-infrared optical imaging modalities for early detection of breast cancer, and (b) assessment of aggressiveness of tumor growth using an animal model. The research plan was organized such that work on developing the optical imaging modality would be undertaken early on, while the work on animal model would begin in the third year of the project.

Consequently, the work on development of non-invasive near-infrared optical imaging modalities for early detection of breast cancer (*Specific Aim 4*) started during the current reporting period. This research builds on and extends the work that the CCNY group has been pursuing.

The goal of the research is to develop optical spectroscopy and imaging approaches that use the near-infrared (800-1300 nm) light to obtain three-dimensional (3-*D*) tomographic images of human breast that enable detection, localization, and possible diagnosis of tumor(s) in the breast. The work at the developmental stage would be carried out on phantoms that have optical absorption, emission, and scattering properties similar to breast tissues, and on realistic breast models assembled using *ex vivo* breast tissues. Prior to carrying out research involving *ex vivo* human breast tissues, we secured regulatory approval from both the Internal Review Board at CCNY and from USAMRMC (*Specific Aim 4, Task #13*).

The optical imaging approach that we are pursuing is known as optical tomographic imaging using independent component analysis (OPTICA).[1-4] The experimental arrangement for OPTICA uses multi-source illumination of sample under investigation, and multi-detector transillumination signal acquisition. We modified and upgraded the experimental arrangement (*Specific Aim 4, Task #14*). The pump source for the Ti:sapphire laser oscillator operating over the 750-850 nm range was changed from the aging Ar-ion laser to diode-pumped Nd:YAG laser (second harmonic at 532 nm). This change of pump source ensures lower noise, higher stability, and reduced fluctuations in Ti:sapphire laser output that are essential for imaging experiments. A sensitive 1392 X 1040 pixels CCD camera was acquired for signal acquisition.

To start with, we used the OPTICA approach to study a model cancerous breast assembled using *ex vivo* human breast tissues (*Specific Aim 4, Task #15 and Task #16*). Details of the theoretical background, numerical algorithm, experimental arrangement, and key results are presented in *Appendix 2:* "Optical diffuse imaging of an *ex vivo* model cancerous human breast using independent component analysis," *IEEE J. Select. Topics Quantum Electron.* **14**, 43 (2008). We provide a brief overview of the work and key results in the following paragraphs, and refer to *Appendix 2* for details.

The model cancerous breast used in this study was a 70 mm X 55 mm X 33 mm slab composed of two pieces of *ex vivo* human breast tissues provided to us by National Disease Research Interchange under an Internal Review Board approval at the City College of New York. The larger piece was normal tissue that included mainly adipose tissue and streaks of fibro-glandular tissues. The existence of the fibro-glandular tissues was not known prior to making the measurements. The second piece was mainly a tumor (infiltrating ductal carcinoma) with a small amount of normal tissues in the margins with an overall approximate dimension of 8 mm X 5 mm X 3 mm. An incision was made in the mid-plane (along the *z*-axis, which was the shorter dimension of the tissue) of the normal piece and some amount of normal tissue was removed from the central region making a small pouch. The tumor piece was then inserted into

the pouch and the incision was closed by moderate compression of the composite consisting of the normal tissue and the tumor along *x-y-z* directions. The breast tissue slab was contained inside a transparent plastic box. One of the sides of the box could be moved to uniformly compress the tissue along the *z*-axis and hold it in position. The resulting specimen, a 70 mm X 55 mm X 33 mm slab, was treated as one entity in the subsequent imaging experiment. The position of the tumor within the slab was known since it was placed in position as discussed above. One of the tests of the efficacy of this imaging approach was to see how well the known position is assessed.

The experimental arrangement (shown schematically in Fig. 1(a) of *Appendix 2*) used a 200-μm optical fiber to deliver a 784-nm, 300 mW continuous-wave beam from a diode laser for sample illumination. The beam was collimated to a 1-mm spot onto the entrance face (the 'source plane') of the slab sample. Multiple source illumination was realized in practice by step scanning the slab sample across the laser beam in a 22X 16 *x-y* array of grid points with a step size of 2.0 mm using a computer controlled translation stage. The signal from the opposite face of the sample (the 'detection plane') was collected by a camera lens and projected onto the sensing element of a cooled 16-bit, 1024 X 1024-pixel charged couple device (CCD) camera. Although the scanned area is 42 mm X 30 mm on the source plane, the imaged area of the detection plane was much larger, covering the entire 70 mm X 55 mm area of the model breast. Each illuminated pixel of the CCD camera could be regarded as a detector.

For illumination of each scanned point, the CCD camera recorded an image. A typical raw image is shown in Fig. 1(c) of *Appendix 2.* Each raw image was then cropped to select out the information-rich region, and binned to enhance the signal-to-noise ratio. All the binned images corresponding to illumination of the grid points in sequence were then stacked, and used as input for independent component analysis. The details of the analysis method, theoretical formalism, target localization algorithm, and experimental arrangement have been published, [4] and are presented in *Appendix 2*. After optical measurements, the sample was transferred to our collaborators at the New York Eye and Ear Infirmary for pathological study and correlation.

The key results of the study are as follows.

(a) OPTICA identified three different structures (Fig. 2, *Appendix 2*) that include the tumor whose presence and position were known from the sample preparation process. We ascribed the other two structures to fibro-glandular tissues, since the remainder of the model breast mainly consisted of adipose tissue. Comparison with the pathology results further confirmed the identity of the tumor and the fibro-glandular tissues.

(b) The location of the tumor was determined to within ~1 mm in all three dimensions. The locations of the fibro-glandular tissues were also estimated. The locations of the components are given in Table I of *Appendix 2*.

(c) The FWHM of the tumor is estimated to be ~ 10.3 mm and 7.4 mm along the *x* and *y* directions, respectively (details in Fig. 3, *Appendix 2*).

6. KEY ACCOMPLISHMENTS

- The key training accomplishment includes successful beginning of the training of physical scientists and engineers of CCNY research team in the biology, biochemistry, genetics and pharmacological aspects of breast cancer research.

- A key research accomplishment involve demonstration of the efficacy of Optical Tomography using Independent Component Analysis (OPTICA) approach for detection, 3-*D* localization, and cross section imaging of a tumor inside a realistic breast model composed of excised breast tissues was determined with millimeter accuracy (*Appendix 2*).

7. REPORTABLE OUTCOMES

Journal Articles

1. M. Xu, M. Alrubaiee, S. K. Gayen and R. R. Alfano, "Optical diffuse imaging of an *ex vivo* model cancerous human breast using independent component analysis," *IEEE J. Select. Topics Quantum Electron.* **14**, 43 (2008).

Presentations

2. S. K. Gayen, M. Alrubaiee, M. Xu, and R. R. Alfano, "Optical imaging of an *ex vivo* model cancerous human breast using independent component analysis." Poster P40-6 presented at the *Era of Hope*, Department of Defense Breast Cancer Research Program Meeting, June 25-28, 2008, Baltimore, Maryland. Abstract appears in p. 281 of Meeting Proceedings.

8. CONCLUSION

The work carried out during this reporting period: (a) initiates the training of CCNY research team in biological and medical aspects of breast cancer research; and (b) shows the potential for noninvasive detection and three-dimensional localization of a tumor within a breast with significant accuracy based on the differences in the light scattering and absorption characteristics of the tumor and normal breast tissue.

"***So What Section***"

- The National Cancer Institute (NCI) has identified the development of imaging methodologies as an extraordinary opportunity for advancement in cancer research. Since the background of the CCNY team is in physical sciences and engineering, the training they received would provide them with necessary background in the biology of cancer research, and help develop a knowledgeable multidisciplinary research force in the fight against breast cancer.
- A recent study involving 35,319 patients underscores the influence of primary tumor location on breast cancer prognosis, and makes it imperative that breast cancer detection modalities obtain three dimensional (3-*D*) location of the tumor relative to the axilla.[5] The current work is an important development in obtaining 3-*D* location of a tumor within the breast.
- The study of model cancerous breast assembled using *ex vivo* breast tissues is important and essential for the next step, *in vivo* optical breast imaging involving volunteers.

9. REFERENCES

1. M. Xu, M. Alrubaiee, S. K. Gayen and R. R. Alfano, "Three-dimensional optical imaging of objects in a turbid m edium using inde pendent component analysis: theory and simulation," *J. Biomed. Opt.* **10**, 051705 (2005).
2. M. Alrubaiee, M. Xu, S. K. Gayen, M. Brito, and R. R. Alfa no, "Three-dimensional optical tomographic imaging of objects in tissue-simulating turbid m edium using independent component analysis," *Appl. Phys. Lett.* **87**, 191112 (2005).
3. M. Alrubaiee, M. Xu, S. K. Gayen, and R. R. Alfano, "Three-dim ensional localization and cross section reconstructi on of fluorescent targets in *ex vivo* breast tissue using independent component analysis," *Appl. Phys. Lett.* **89**, 133902 (2006).
4. M. Xu, M. Alrubaiee, S . K. Gayen and R. R. Alfano, "Optical diffuse im aging of an *ex vivo* model cancerous hum an breast using independent component analysis," *IEEE J. Select. Topics Quantum Electron.* **14**, 43 (2008).
5. N. Kroman, J. Wohlfahrt, H. T. Mouridsen, and M. Melbye, "Influence of tum or location on breast cancer prognosis," *Int. J. Cancer* **105**, 542 -545 (2003).

10. APPENDICES

Appendix 1. Outlines of the courses taken by the trainees

Appendix 2. M. Xu, M. Alrubaiee, S. K. Gaye n and R. R. Alfano, "Optical diffuse imaging of an *ex vivo* model cancerous hum an breast using independent component analysis," *IEEE J. Select. Topics Quantum Electron.* **14**, 43 (2008).

Biochemistry Core Course, 2007 - Fall Semester

Lectures will be held in A-950 (Weill Cornell Medical College) from 10:30AM-12PM.
Review sessions on Fridays in E-115 from 4:00-6:00PM.

Course Directors: Dimitar Nikolov nikolovd@mskcc.org 212-639-6784
Min Lu mlu@med.cornell.edu 212-746-6562
Course TA's: Jaclyn Gareau, Nikhil Singla, Sumana Sanyal

Recommended Texts:
1) Fersht, Structure and Mechanism in Protein Science
2) Cantor and Schimmel, Biophysical Chemistry, Part II
3) von Holde, Johnson and Ho, Principles of Physical Biochemistry

#	Dates	Day		Lecturer	TA	Room
1	9/10	M	Thermodynamics-I	O. Boudker	J. Gareau	A-950
2	9/12	W	Thermodynamics-II	O. Boudker	J. Gareau	A-950
3	9/14	F	Thermodynamics-III	O. Boudker	J. Gareau	A-950
4	9/17	M	Kinetics (transducin), MM	T. Ryan	J. Gareau	A-950
5	9/19	W	Rate limiting steps, diffusion	T. Ryan	J. Gareau	A-950
6	9/21	F	Protein purification	S. Shuman	J. Gareau	A-950
7	9/24	M	Protein purification (methods, assays)	S. Shuman	J. Gareau	A-950
8	9/26	W	Protein purification	S. Shuman	J. Gareau	A-950
9	9/28	F	High Throughput Screening	H. Djaballah	J. Gareau	A-950
10	10/1	M	Ligand binding	H. Djaballah	J. Gareau	A-950
11	10/3	W	Enzymes, why do they work?	C. Lima	N. Singla	A-950
12	10/5	F	Transition states	C. Lima	N. Singla	A-950
13	10/8	M	Reaction pathways (proteases, phosphatases)	C. Lima	N. Singla	A-950
			Test 1 covering lectures 1-13 distributed 10/8 – due back 10/15			
14	10/10	W	Physical basis for NMR	D. Eliezer	N. Singla	A-950
15	10/12	F	NMR resolves a biological problem	D. Eliezer	N. Singla	A-950
16	10/15	M	Physical basis for Mass Spectrometry	P. Tempst	N. Singla	A-950
17	10/17	W	Use of Mass Spec in resolving a biological problem	P. Tempst	N. Singla	A-950
18	10/19	F	Physical basis for diffraction	H. Wu	N. Singla	A-950
19	10/22	M	Applications for Crystallography	H. Wu	N. Singla	A-950
20	10/24	W	Where has Crystallography resolved a problem?	H. Wu	N. Singla	A-950
21	10/26	F	Physical basis of Spectroscopy	M. Lu	N. Singla	A-950
22	10/29	M	Biological applications for spectroscopy	M. Lu	N. Singla	A-950
23	10/31	W	Protein stability	D. Nikolov	N. Singla	A-950
24	11/2	F	Protein stability	D. Nikolov	N. Singla	A-950
25	11/5	M	Protein Folding	D. Eliezer	N. Singla	A-950
26	11/7	W	Protein Folding	D. Eliezer	N. Singla	A-950
			Test 2 covering lectures 14-26 distributed 11/7 – due back 11/14			
27	11/9	F	Bioinformatics	J. Vilar	N. Singla	E-115
28	11/12	M	Computational Approaches to Structure	J. Vilar	N. Singla	A-950
29	11/14	W	Computational Approaches to Structure	J. Vilar	N. Singla	A-950
30	11/16	F	Protein-protein recognition & specificity	J. Goldberg	S. Sanyal	A-950
31	11/19	M	Protein-protein recognition & specificity	J. Goldberg	S. Sanyal	A-950
32	11/26	M	Protein-protein recognition & specificity	J. Goldberg	S. Sanyal	A-950
33	11/28	W	Biochemistry of lipids	A. Menon	S. Sanyal	A-950
34	11/30	F	Biochemistry of lipids	A. Menon	S. Sanyal	A-950
	13/3	M	no lecture			
35	12/5	W	Lipid and membrane structure	F. Maxfield	S. Sanyal	A-950
36	12/7	F	Lipid and membrane dynamics	F. Maxfield	S. Sanyal	A-950
37	12/10	M	Application of single-molecule science	S. Blanchard	S. Sanyal	A-950
38	12/12	W	Applications of single-molecule science	S. Blanchard	S. Sanyal	A-950
			Test 3 for lectures 27-38 distributed 12/12 – due back 12/19 – Patel's questions will be distributed separately			
39	12/14	F	Structural biology of nucleic acids	D. Patel	S. Sanyal	A-950
40	12/17	M	DNA-RNA-protein interactions	D. Patel	S. Sanyal	A-950
41	12/19	W	DNA-RNA-protein interactions	D. Patel	S. Sanyal	A-950

Molecular Genetics
Fall 2007
General Information

Course Director:

Scott Keeney s-keeney@ski.mskcc.org

Teaching Assistants:

Ryan Kniewel ryk2001@med.cornell.edu
Emily Marcinkevicius emm2009@med.cornell.edu
Kate Rochlin kmr2006@med.cornell.edu
Drew Thacker dft2001@med.cornell.edu

Readings:

Readings will be from the primary literature. You may also wish to refer to a basic genetics text in some instances. Several textbooks (including *An Introduction to Genetic Analysis* by Griffiths et al and *Human Molecular Genetics 2* by Strachan and Read) are available online through Pubmed:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books

Additionally, the following textbooks have been placed on reserve in the MSK library:
Genes 8, by Benjamin Lewin
Genetics: Analysis of Genes and Genomes, by Daniel Hartl and Elizabeth Jones

Useful websites:

NCBI: http://www.ncbi.nlm.nih.gov/
E. coli: http://genolist.pasteur.fr/Colibri/
S. cerevisiae genome database: http://www.yeastgenome.org/
S. pombe genome database: http://www.sanger.ac.uk/Projects/S_pombe/
Drosophila genetics: http://flybase.bio.indiana.edu/
C. elegans: http://www.wormbase.org/
Zebra fish: http://zfin.org
Mouse genetics: http://www.informatics.jax.org/
Ensembl mouse genome server: http://www.ensembl.org/Mus_musculus/
Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Human genome browser: http://genome.cse.ucsc.edu

Molecular Genetics
Fall 2007 Tu, Th 10-11:30. Room RRL-101 (except Sept. 6).

Lecture schedule

Tu Sept 4	Organizational meeting	Scott Keeney
Th Sept 6	1. *C. elegans* Genetics 1	Jen Zallen (RRL-116)
Tu Sept 11	2. *C. elegans* Genetics 2	Jen Zallen
Th Sept 13	3. Diploid genetics: Genes and genomes	Kathryn Anderson
Discussion section 1: Lectures 1-2		
Tu Sept 18	4. Diploid genetics: Linkage mapping	Kathryn Anderson
Th Sept 20	5. Diploid genetics: Mutagenesis and genetic screens	Kathryn Anderson
Discussion section 2: Lectures 3-4		
Tu Sept 25	6. Forward and reverse genetics in yeast 1	Xiaolan Zhao
Th Sept 27	7. Forward and reverse genetics in yeast 2	Xiaolan Zhao
Discussion section 3: Lectures 4-5		
Tu Oct 2	8. Tetrad analysis	Scott Keeney
Th Oct 4	9. Recombination mechanisms	Scott Keeney
Discussion section 4: Lectures 6-7		
Tu Oct 9	10. Micro RNAs and RNAi, part 1	Jidong Liu
Th Oct 11	11. Micro RNAs and RNAi, part 2	Eric Lai
Discussion section 5: Lectures 8-9		
Tu Oct 16	12. Applied genetic analysis in *Drosophila*, part 1	Monn Myat
Th Oct 18	13. Applied genetic analysis in *Drosophila*, part 2	Monn Myat
Discussion section 6: lectures 10-11		

Tu Oct 23	14. Cytogenetics	Raju Chaganti
Th Oct 25	15. Transposable elements	Scott Keeney
Discussion section 7: Lectures 12-13		

Take-home exam 1: Oct. 25–29 (material covered through Oct. 18)

Tu Oct 30	16. Introduction to genetic analysis in the mouse	Liz Lacy
Th Nov 1	17. ES cell technology and engineering mutations	Kat Hadjantonakis
Discussion section 8: Lectures 14-15		
Tu Nov 6	18. Screens and linkage mapping in mouse	Kathryn Anderson
Th Nov 8	19. The mouse genome	Liz Lacy
Discussion section 9: Lectures 16-17		

Tu Nov 13	20. Chromosome rearrangements	Maria Jasin
Th Nov 15	21. Imprinting and X chromosome inactivation	Liz Lacy
Discussion section 10: Lectures 18-19		
Tu Nov 20	22. Human genetics 1	Robert Klein
Th Nov 22	Thanksgiving. No lecture	
No discussion section		
Tu Nov 27	23. Human genetics 2	Robert Klein
Th Nov 29	24. Cancer genetics 1	Johanna Joyce
Discussion section 11: Lectures 22-23		
Tu Dec 4	25. Cancer genetics 2	Anna Kenney
Th Dec 6	26. Genomic approaches	Dirk Schnappinger
Discussion section 12: Lectures 24-25		

<u>Applied genetic analysis: signaling pathways in mouse</u>

Tu Dec 11	27. Signaling pathways in limb development	Licia Selleri
Th Dec 13	28. Pbx Hox cofactors in limb development	Licia Selleri
Discussion section 13: Lectures 26-28		

Take Home Exam 2: Dec. 14–20 (material from Oct. 23 to Dec. 13)

CELL BIOLOGY AND DEVELOPMENT: Qtrs III and IV Spring 2008

Course Directors:	Phone		e-mail
Dr. Marilyn Resh	RRL817C	639-2514	m-resh@ski.mskcc.org
Dr. Ching-Hwa Sung	LC312	746-2291	chsung@med.cornell.edu
Dr. Thomas Sato	A512	746-6013	tns2003@med.cornell.edu
Dr. Mary Baylies	RRL1001B	639-5888	m-baylies@ski.mskcc.org

Lectures: Tuesdays and Thursdays, 10 AM – 12 noon, RRL 117; unless otherwise noted.

Discussion Sections: Fridays, 2-3:30 pm, RRL 614 and RRL 301
The class will be split in half; you will be assigned to either RRL614 or RRL 301

*****Note: Attendance at Discussion Section is MANDATORY!!*****

REQUIRED TEXTBOOK: Molecular Biology of the Cell
Fifth Edition (Note: New Edition!)
Alberts et al
Garland Publishing

Graduate Teaching Assistants:	Phone	e-mail
John Buglino	639-2551	job2005@med.cornell.edu
Wendy See	639-2551	wls2003@med.cornell.edu
Mary Madabushi	639-8661	meb2013@ med.cornell.edu
Athea Vichas	639-2784	atv2002@med.cornell.edu

Cell Biology and Development: Spring 2008

Date	Topic	Lecturer
I.	**Cell Structure and Function**	
1/8	Membrane Structure and Function	Katherine Hajjar
1/10	Translocation of Proteins Across Membranes	Sandy Simon (RU)
1/11	Discussion	TA's
1/15	Biosynthetic pathways: cellular compartments	Anna Muesch (Albert Einstein)
1/17	Nuclear Transport	Mike Rout (RU)
1/18	Discussion	TA's
1/22	Mitochondria	Giovanni Manfredi
1/24	Endocytic membrane trafficking	Tim McGraw
1/25	Discussion	TA's
1/29	Ubiquitin pathway and the proteasome	Amy Lam
1/31	Polarized trafficking and cell polarity	Enrique Rodgriguez-Boulan
2/1	Discussion	TA's
2/5	Cell matrix	Carl Blobel
2/7	Microtubules and motors	Geri Kreitzer
2/8	Discussion	TA's
2/12	Actin based motility	Alan Hall
2/14	Cell-cell contact	Elaine Fuchs(Ben Short/Danelle Devenport, RU)
2/15	***Review Session***	TA's
2/19	***EXAM I***	***RRL AUDITORIUM***
2/21	***Graduate School Interview Day***	No class

II. Receptors and Signaling

Date	Topic		Lecturer
2/26	Aging and Growth Factor Signaling		Makoto Kuro-o (UT Southwestern)
2/28	Apoptosis and Autophagy	*****RRL-103*****	Xuejun Jiang
2/29	Discussion Section	TA's	
3/4	Receptor Ser/Thr Kinases I	Joan	Massague
3/6	Receptor Ser/Thr Kinases II	"	
3/7	Discussion Section	TA's	
3/11	Tyrosine Kinase Receptors and Oncoproteins I		Marilyn Resh
3/13	Tyrosine Kinase Receptors and Oncoproteins II	*****RRL-103*****	"
3/14	Discussion Section	TA's	
3/18	G protein Signaling I	Xin-Yun	Huang
3/20	G protein Signaling II		"
3/21	Discussion Section	TA's	
3/25	Cellular Mechanotransduction		Cynthia Reinhart-King (Cornell, Ithaca)
3/27	Wnt signaling	Tony	Brown
3/28	Discussion Section	TA's	
4/1	Notch signaling	Eric	Lai
4/3	Hedgehog signaling	Stewart	Anderson
4/4	Discussion Section		
4/8	***Review Session***		TA's
4/10	***EXAM II***		***RRL AUDITORIUM***
4/11	No discussion groups		

III. Development – Cell Biology in the context of an organism

Date	**Topic**	**Lecturer**
4/15	Introduction to Concepts in Development	Mary Baylies
4/17	Imaging Approaches in Developmental Biology and Model systems	Kat Hadjantonakis Brian Richardson
4/18	Discussion	TAs
Week of 4/21	***Spring Break***	
4/29	no class	
5/1	Force and Form in Development: actin-myosin regulation during Drosophila cellularization and gastrulation	Jen Zallen
5/2	Discussion	TAs
5/6	***DuVigneaud Symposium***	***No Class***
5/8	Lineage Specification in the Mouse embryo	Kat Hadjantonakis
5/9	Discussion	TAs
5/13	Axis Determination in the Mouse embryo	Kathryn Anderson
5/15	Cell-cell fusion during Muscle Development in Drosophila and Mouse	Mary Baylies
5/16	Discussion	TAs
5/20	Asymmetric Division and Migration in the developing Mammalian CNS	Song Hai Shi
5/22	Cerebellum Development and Morphogenesis	Alex Joyner
5/23	Discussion Section	TAs
5/27	Repair and Maintenance of organ systems with Stem cells	Lorenz Studer
5/29	***Review session***	
6/3	***EXAM III***	***RRL Auditorium***

PRINCIPLES of PHARMACOLOGY
Quarter III 2008

Course Director: Roberto Levi (LC-419; 746-6223)
Assistant Director: Lonny Levin (E-505, 746-6752)

Lectures are Mondays, Wednesdays, and Fridays
9:00 am – 10:30 AM

E 415

Module I. General Principles

Week 1

Mon. 2/11	Absorption, Distribution and Biotransformation	Dr. C.E. Inturrisi
Wed. 2/13	Molecular Biology of Transporters in ADME[1]	Dr. Anthony Sauve
Fri. 2/15	Pharmacokinetics – General Concepts	Dr. C.E. Inturrisi

Week 2

Mon. 2/18	Presidents' Day	
Wed. 2/20	The Cytochromes P-450 Gene Family	Dr. A.B. Rifkind
Fri. 2/22	GSMS Recruitment	

Week 3

Mon 2/25	Receptor Theory	Dr. G. Pasternak
Wed. 2/27	Pharmacogenetics – Adverse drug Reactions	Dr. M. Reidenberg
Fri. 2/29	FIRST TEST (weeks 1-3 = 6 lectures)	

Module II. Nervous and Circulatory Systems

Week 4

Mon. 3/3	Cardiovascular Physiology	Dr. Thomas Maack
Wed. 3/5	Cholinergics	Dr. R. Levi
Fri. 3/7	Anesthetics	Dr. H. Hemmings

Week 5

Mon. 3/10	Adrenergics	Dr. R. Levi
Wed. 3/12	Anti-Ischemics	Dr. R. Levi
Fri. 3/14	Heart Failure Drugs	Dr. P. Heerdt

[1] Absorption, Distribution, Metabolism and Elimination

Week 6

Mon. 3/17	Diuretics	Dr. L.R. Levin
Wed. 3/19	Antiarrhythmics	Dr. G. Abbott
Fri. 3/21	Antihypertensives	Dr. R. Levi

Week 7

Mon. 3/24	Review session	Dr. R. Levi
Wed. 3/26	SECOND TEST (weeks 4-6 = 9 lectures)	
Fri. 3/28	Anticoagulants & thrombolytics	Dr. A.B. Rifkind

Module III. Host Defense, Inflammation and Endocrine System

Week 8

Mon. 3/31	Anti-Inflammatory Drugs: Nonsteroidals	Dr. A.B. Rifkind
Wed. 4/2	Insulin & Hypoglycemics	Dr. A.B. Rifkind

Week 9

Mon. 4/7	Antibiotic resistance: Staying ahead of the game	Dr. L.J. Gudas
Wed. 4/9	Anti-Ulcer Drugs	Dr. H.H. Szeto
Fri. 4/11	Antihyperlipidemic drugs	Dr. M.M. Reidenberg

Week 10

Mon. 4/14	HIV and anti-virals	Dr. Roy (Trip) Gulick
Mon. 4/14 @ 10:30 am	Contraceptives	Dr. Lee Kraus
Wed. 4/16	Antifungals	Dr. L.R. Levin
Fri. 4/18	THIRD TEST (weeks 7-10 = 9 lectures)	

QUARTER IV - 2008-MOLECULAR PHARMACOLOGY OF CANCER COURSE
COURSE DIRECTORS: DRS. DAVID SCHEINBERG AND YUEMING LI
LECTURES ARE HELD MONDAYS, WEDNESDAYS AND FRIDAYS
1:30 TO 3:00 PM IN ROOM ZRC 1870 (18th FLOOR)
ZUCKERMAN RESEARCH CENTER
415/417 EAST 68TH STREET

DATE	SPEAKER	TOPIC
Monday, 4/28	Drs. Li & Scheinberg	Organizational Meeting
Wednesday, 4/30	Lorraine Gudas	Overview of Anti-Cancer Agents
Friday, 5/2	**No Class**	**Pharmacology Retreat - SKYTOP Lodge**
Monday, 5/5	Paraskevi Giannakakou	Introduction to Cancer Biology
Wednesday, 5/7	Lorraine Gudas	Cancer Stem Cells
Friday, 5/9	Lorraine Gudas	Principles of Angiogenesis Therapy
Monday, 5/12	Richard Kolesnick	Cell Death and Apoptosis in Cancer
Wednesday, 5/14	Samie Jaffrey	Proteonomics and Genomics of Cancer
Friday, 5/16	Derek Tan	Natural Products as Anti-Cancer Drugs
Monday, 5/19	Paraskevi Giannakakou	Drug Resistance
Wednesday, 5/21	Luca Cartegni	RNA Splicing in Cancer
Friday, 5/23	Zvi Fuks	Principles of Radiobiology and Radiation Induced Death
Monday, 5/26	**No Class**	**Memorial Day**
Wednesday, 5/28	Neal Rosen	Principles of Targeting Signal Transduction in Cancer Therapy
Thurs-Frid 5/29-5/30		**Mid Term Exam**
Monday, 6/2	Gabriela Chiosis	Proteins and Protein Chaperones as Cancer Targets
Wednesday, 6/4	Phil Livingston	Activating the Humoral Response for Cancer therapy
Friday, 6/6	Steven Larson	Principles of Imaging in Cancer Therapy
Monday, 6/9	David Scheinberg	Antibody Therapy of Cancer
Wednesday, 6/11	David Scheinberg	T Cell Vaccines In Cancer
Friday, 6/13	Stephen Nimer	Transcription Factors and Oncogenes as Targets for Cancer Therapy
Monday, 6/16	Renier Brentjens	Engineered Cells as Drugs and Gene Therapy

PAGE TWO - MOLECULAR PHARMACOLOGY OF CANCER COURSE		
Wednesday, 6/18	Anthony Sauve	Chemical Carcinogenesis
Friday, 6/20	Zhiqiang An (Merck)	Proteins Displayed on Phage as a Drug Source for Cancer Therapy
Monday, 6/23	Yueming Li	Proteases and Cancer
Wednesday, 6/25	Hakim Djaballah	Small Molecule Screening: The Gateway to Drug Discovery
Thurs-Frid 6/26-6/27		**Final Exam**

Molecular Imaging Lectures

Time: **Tuesday 5-6pm**
Location: **Selby Conference Room, Department of Radiology**

An overview will be provided of molecular imaging methodologies from the cellular to the "whole human" level. The emphasis will be on experimental imaging, the biochemical pathways and gene expression systems, which can be imaged that are relevant to oncology. The course is intended as an introductory overview of the major methodologies used for experimental molecular imaging, illustrated with specific examples of phenotypic and genotypic imaging. Examples will be drawn from Nuclear, MRI/MRS and optical imaging methodologies. The planned lecture series for 2007-2008 is as follows:

DATE	LECTURE TITLE	LECTURER
2007		
Oct 2	Overview of small animal imaging devices	Pat Zanzonico
Oct 9	Moved to Oct.16th	
Oct 16	Quantitative clinical imaging with FDG	Tim Akhurst
Oct 23	Antibody therapy of metastatic neuroblastoma in bone marrow and CNS	Nai-Kong Cheung
Oct 30	Make-up for missed seminar	
Nov 6	Molecular and systems in pathology	Carlos Cordon-Cardo
Nov 13	No lecture (moved to Feb.12th)	
Nov 20	Uses of viral vectors for the treatment of cancer	Yuman Fong
Nov 27	Thanksgiving week	
Dec 4	Photodynamic therapy	Hans Gerdes
Dec.11	Lecture moved to January 22	
Dec 18	Brain tumor models	Eric Holland
Dec 25	Holiday break	
2008		
Jan 1	Holiday break	
Jan 8	Cell Death	Richard Kolesnick
Jan 15	Molecular tracer in the nuclear medicine clinic	Steve Larson
Jan 22	Computers in Imaging	Peter Kijewski
Jan 29	Overview: Functional MRI of the brain	Andrei Holodny
Feb 5	No seminar – moved to Feb.19	
Feb 12	Molecular-based therapies for thyroid cancer	James Fagin
Feb 19	In vivo molecular imaging technologies (Hoffman Auditorium)	Simon Cherry
Feb 26	The philosophy and practice of targeted antibody therapies	Jorge A. Carrasquillo
Mar 4	Imaging tumor hypoxia	John Humm

Mar 11	Novel approaches to targeting alpha-emitters	David Scheinberg
Mar 18	Postponed to May 20	Vladimir Ponomarev
Mar 25	Hsp90 as a therapeutic target	Neal Rosen
Apr 1	The future of gene therapy	Michel Sadelain
Apr 8	Cross-species comparisons of cancer signaling.	Charles Sawyer
Apr 15	Clinical MR imaging of prostate cancer	Hedvig Hricak
Apr 22	Imaging immune responses to cancer	David Schaer
Apr 29	Development of Cell Cycle Agents for Cancer Therapeutics: New Opportunities of Molecular Imaging	Gary Schwartz
May 6	Response measures in radiology	Lawrence Schwartz
May 13	Robotics in Surgery	Stephen Solomon
May 20	Principles of reporter gene imaging	Vladimir Ponomarev

Optical Diffuse Imaging of an *Ex Vivo* Model Cancerous Human Breast Using Independent Component Analysis

Min Xu, Mohammad Alrubaiee, S. K. Gayen, and R. R. Alfano, *Fellow, IEEE*

***Abstract*—Optical imaging using independent component analysis (OPTICA) has been used for detection, 3-D localization, and cross-section imaging of a tumor inside a model human breast composed of *ex vivo* human breast tissues. OPTICA uses a multisource target illumination and multidetector signal acquisition scheme to obtain multiple spatial and angular views of the sample for target localization. Independent component analysis of the perturbations in the spatial light intensity distribution measured on the sample boundary sorts out the signal originating from individual targets. A back-projection technique estimates the cross-section of each target. The approach correctly provided the positions of a tumor located at the mid-plane and two glandular structures located at different positions within the 33-mm-thick model breast. The reconstructed cross-section images are in good agreement with known dimensions of the structures, and pathological findings.**

***Index Terms*—Breast cancer, diffuse optical imaging, independent component analysis, near infrared (NIR) imaging, optical mammography, optical imaging using independent component analysis (OPTICA).**

I. Introduction

NEAR-INFRARED (NIR) diffuse optical tomography (DOT) is an emerging technology for functional characterization of biological tissues, and has been actively investigated to image lesions in human body organs, such as human breast [1]–[3], brain [4]–[7], and joints [8], [9]. A state-of-the-art DOT illuminates the sample (consisting of targets embedded in a turbid medium) with NIR light, measures the emergent light on the boundary of the turbid medium, and uses an iterative image reconstruction method for repeatedly solving the forward model of light propagation in the medium with an updated estimation of its optical properties to match the detected light intensities. This problem of imaging targets in a turbid medium is an ill-posed inverse problem, and *a priori* knowledge about the optical properties of the medium need to be used to obtain a unique solution at a cost of reduced resolution [10]–[13]. Various prior information such as anatomical structures obtained from X-ray or magnetic resonance imaging (MRI) and the absorption spectra of chromophores have been used to improve the imaging quality of the DOT [14]–[16]. The iterative image reconstruction is computation time intensive and reconstruction in 2-D planar sections instead of a 3-D volume is commonly practiced. Noniterative approaches have also been pursued [17]–[19]. Irrespective of these developments, reconstruction of images with adequate spatial resolution and accurate localization and characterization of the targets remain a formidable task.

We have developed an alternative approach for optical imaging using independent component analysis (OPTICA) [18], [20] that uses a multisource sample illumination and multidetector signal acquisition scheme to generate an extensive data set providing a variety of spatial and angular views of the medium. The signals from individual targets within the interrogated medium are then sorted out by using independent component analysis (ICA) based on their statistical independence. ICA is a statistical technique from information theory that is able to recover independent signals from their measured mixtures [21], [22]. ICA has been successfully applied in many biomedical applications, such as electroencephalogram (EEG) [23] and functional magnetic resonance imaging (fMRI) [24], and has been shown to be effective in separating signals from different brain activity centers. In DOT, excess light absorption or scattering by the individual targets embedded in the medium serve as the source of independent signals whose weighted mixture is recorded by a detector on the boundary of the medium. Since an independent component originating from any particular target relates directly to how light propagates from the source to the target and from the target to the detector, the recovered independent components can serve as the starting point for 3-D localization and optical characterization of individual targets in the medium. Such a staged procedure has been shown to significantly improve the sensitivity to small/weak absorptive, scattering and/or fluorescent targets, and can achieve a 3-D localization of the targets with remarkable accuracy and resolution [18], [25], [26].

The independent component is proportional to the strength of the target (the product of the difference in the absorption/scattering coefficient between the target and the background, and the volume of the target) and the convolution of the light propagators from the source to the target and from the

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target to the detector. The two light propagators can be deconvoluted in the Fourier space. A 2-D cross-section image of the target is obtained by back projecting the independent component onto the transversal plane at the axial location of the target. Every independent component retrieved by ICA represents the signal from only one target with localization determined from earlier stage of analysis. So, a back projection formalism with little or no regularization can be applied to obtain a cross-section image of the target with improved spatial resolution than what is feasible in a conventional DOT.

We have previously tested the efficacy of OPTICA on samples consisting of absorbing or scattering targets within tissue phantoms and fluorescent targets in *ex vivo* tissue [18], [25], [26]. In this paper, we use OPTICA to investigate a tumor and other structures embedded in a "realistic" model breast assembled using *ex vivo* human breast tissues, as a prelude to *in vivo* breast imaging. The remainder of the paper is organized as follows. Section II presents the theoretical formalism of OPTICA and the back-projection approach for obtaining the cross-section image of a target. Section III describes the experimental arrangement, method, and parameters. Experimental results appear in Section IV. The implications are discussed in Section V.

II. Theoretical Formalism of Optical Imaging Using Independent Component Analysis

The presence of targets (optical inhomogeneities) inside a turbid medium perturbs the spatial intensity distribution of light emergent from the medium under illumination by a probing beam. When illuminated by a point source of unit power, the change in the light intensity distribution on the boundary of the specimen due to absorptive and scattering targets can be written as [27], [28]

$$-\Delta I(\mathbf{r}_d,\mathbf{r}_s)=\int d^3\mathbf{r}\,\delta\mu_a(\mathbf{r})\,cG(\mathbf{r}_d,\mathbf{r})\,G(\mathbf{r},\mathbf{r}_s)+\int d^3\mathbf{r}\,\delta D(\mathbf{r})\,c\nabla_{\mathbf{r}}\,G(\mathbf{r}_d,\mathbf{r})\nabla_{\mathbf{r}}G(\mathbf{r},\mathbf{r}_s)\quad(1)$$

in the first-order Born approximation assuming that light diffuses inside the medium [29]. Here, $\mathbf{r}_s$ and $\mathbf{r}_d$ are the positions of the source and the detector on the boundary, $\delta\mu_a(\mathbf{r})=\mu_a(\mathbf{r})-\mu_{a_0}$ and $\delta D(\mathbf{r})=D(\mathbf{r})-D_0$ are the differences in absorption coefficient and diffusion coefficient, respectively, between the target at $\mathbf{r}$ and the background medium, c is the speed of light in the medium, and $G(\mathbf{r},\mathbf{r}')$ is the Green's function describing light propagation from $\mathbf{r}'$ to $\mathbf{r}$ inside the medium of absorption coefficient μ_{a_0} and diffusion coefficient D_0.

OPTICA assumes each inhomogeneity within the turbid medium to be a virtual source and expresses the change of the light intensity on the boundary of the specimen as

$$-\Delta I(\mathbf{r}_d,\mathbf{r}_s)=\sum_j a_j(\mathbf{r}_d)\,s_j(\mathbf{r}_s)\quad(2)$$

where $s_j(\mathbf{r}_s)$ represents the jth target illuminated by the incident wave at $\mathbf{r}_s$ and $a_j(\mathbf{r}_d)$ is the weighting matrix describing the propagation of light from the jth inhomogeneity to the detector at $\mathbf{r}_d$. Each absorptive inhomogeneity contributes one term in (2), and each scattering inhomogeneity contributes three terms in (2) [18]. The detected change of the light intensity $-\Delta I$ is, hence, a linear mixture of signals where a_j and s_j can now be interpreted as the *j*th weighting matrix and virtual source, respectively. Owing to the statistical independence between these virtual sources, independent component analysis of $-\Delta I$ will yield a list of independent components and recover both a_j and s_j. Here, a_j and s_j are the independent intensity distribution on the detector and source planes, respectively, for the jth target. The number of the leading independent components gives the number of objects. The location of the *j*th target is obtained from the analysis of the retrieved independent component (s_j and a_j) that relates directly to the source-to-object and object-to-detector Green's functions $G(\mathbf{r}_j,\mathbf{r}_s)$ and $G(\mathbf{r}_d,\mathbf{r}_j)$ and the optical property of the target where $\mathbf{r}_j$ is the position of the jth object [18], [20], [25], [26].

For the slab geometry investigated here, there are three virtual sources of specific patterns (one centrosymmetric and two dumbbell-shaped) associated with each scattering inhomogeneity, whereas only one centrosymmetric virtual source is associated with each absorptive inhomogeneity. Among the three virtual sources associated with a scattering inhomogeneity, the centrosymmetric virtual source is the strongest and more amenable to detection in a thick turbid medium [25]. The centrosymmetric virtual source and the corresponding weighting matrix are $s_j\propto G(\mathbf{r}_j,\mathbf{r}_s)$ and $a_j\propto G(\mathbf{r}_d,\mathbf{r}_j)$, and $s_j\propto\partial G/\partial z(\mathbf{r}_j,\mathbf{r}_s)$ and $a_j\propto\partial G/\partial z(\mathbf{r}_d,\mathbf{r}_j)$, respectively, for absorptive and scattering inhomogeneities. A simple least square fitting of the centrosymmetric component, such as

$$\min_{\mathbf{r}_j,\alpha_j,\beta_j}\left\{\sum_{\mathbf{r}_s}\left[\alpha_j^{-1}s_j(\mathbf{r}_s)-G(\mathbf{r}_j,\mathbf{r}_s)\right]^2+\sum_{\mathbf{r}_d}\left[\beta_j^{-1}a_j(\mathbf{r}_d)-G(\mathbf{r}_d,\mathbf{r}_j)\right]^2\right\}\quad(3)$$

for the absorptive object, can be used to yield the 3-D location $\mathbf{r}_j$ and the strength $\alpha_j\beta_j$ of the target. When *a priori* knowledge about the property of the target is not available, (3) can still be used to estimate the 3-D location of the target regardless of the absorption or scattering property of the target. This is due to the fact that $\partial G/\partial z(\mathbf{r}_j,\mathbf{r}_s)\simeq-\kappa G(\mathbf{r}_j,\mathbf{r}_s)$ and $\partial G/\partial z(\mathbf{r}_d,\mathbf{r}_j)\simeq-\kappa G(\mathbf{r}_d,\mathbf{r}_j)$, where $\kappa=\sqrt{(\mu_{a_0}-i\omega/c)/D_0}$ is chosen to have a nonnegative real part with ω the modulation frequency of the incident wave.

The signal from the *j*th target is simply given by $-\Delta I_j=a_j(\mathbf{r}_d)s_j(\mathbf{r}_s)$. On the other hand, the centrosymmetric signal of the *j*th target can be approximated as a double convolution

$$-\Delta I_j(\mathbf{r}_d,\mathbf{r}_s)=\int G(\boldsymbol{\rho}_d-\boldsymbol{\rho},z_d,z_j)\,X_j(\boldsymbol{\rho})\,G(\boldsymbol{\rho}-\boldsymbol{\rho}_s,z_j,z_s)d\boldsymbol{\rho}\quad(4)$$

where the integration is over the $z=z_j$ plane, X_j represents the target, and $\boldsymbol{\rho}_d$ and $\boldsymbol{\rho}_s$ are the lateral coordinates of the detector and the source, respectively. The cross-section image of the *j*th target X_j is a 2-D distribution of the absorption/scattering coefficient of the target on the $z=z_j$ plane. In the Fourier space,

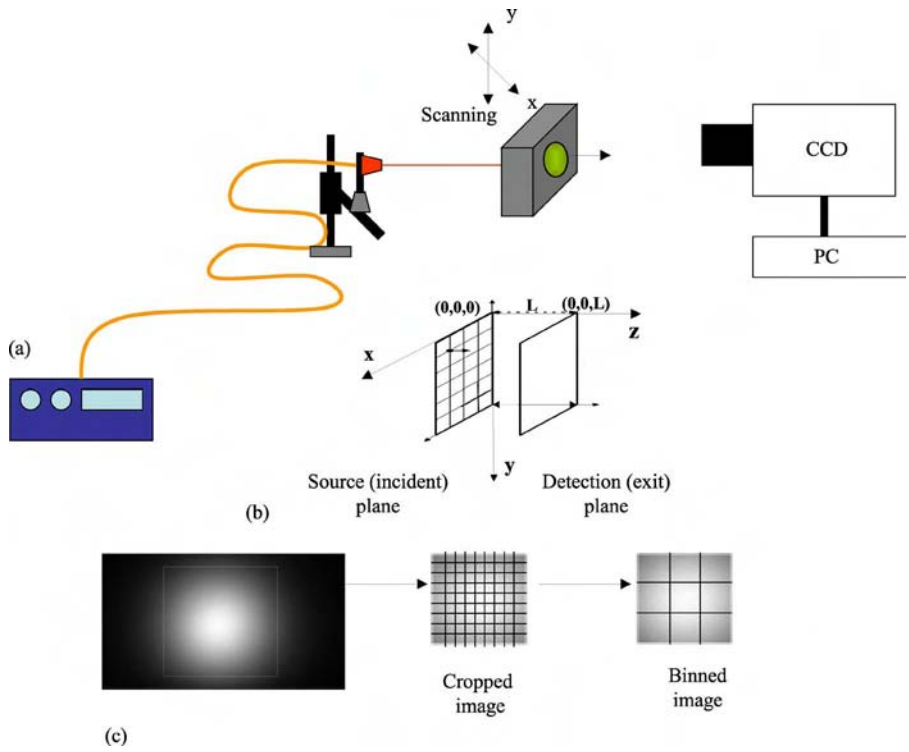

Fig. 1. (a) Schematic diagram of the experimental arrangement. CCD, charge coupled device; PC, personal computer. (b) Expanded view of the sample input (source) plane and exit (detection) plane showing the grid points in the x–y plane. (c) Typical raw CCD image of the detection plane, and how it is cropped and binned for analysis.

the target function X_j can be obtained from (4) as

$$X_j(\mathbf{q}) = -\frac{\Delta I_j(\mathbf{q}-\mathbf{q}_s, \mathbf{q}_s)}{G(\mathbf{q}-\mathbf{q}_s, z_d, z_j)G^*(\mathbf{q}_s, z_j, z_s)} \tag{5}$$

where $\mathbf{q}$ and $\mathbf{q}_s$ are the spatial frequency on the lateral plane and "$*$" denotes complex conjugate. We choose $\mathbf{q}_s = 0$ in the evaluation of the target function (5) since sources are usually much sparser than detectors in our setup where a charge-coupled device (CCD) camera is used to detect the emergent light intensity on the surface of the medium. The inverse Fourier transforms of $X_j(\mathbf{q})$ yields the high-resolution cross-section image of the jth target due to the high density of detecting pixels of the CCD. The size of the target is estimated by the full-width at half-maximum (FWHM) of the cross-section image X_j.

To sum up, OPTICA first detects and retrieves independent components corresponding to each target embedded inside a turbid medium, then obtains the 3-D location and strength of the target from these independent components, further reconstructs the cross-section image of the target on the transversal plane where the target locates, and finally, the size and the optical property of the target are estimated.

III. Experiment

The experimental arrangement for detection and localization of the tumor in the *ex vivo* model breast sample is shown in Fig. 1(a). The model breast was a 70 mm × 55 mm × 33 mm slab composed of excised female human breast tissues provided to us by National Disease Research Interchange under an Internal Review Board approval at the City College of New York. The model breast was assembled using two pieces of *ex vivo* human breast tissues. The larger piece was normal tissue that included mainly adipose tissue and streaks of fibroglandular tissues. The existence of the fibroglandular tissues was not known prior to making the measurements.

The second piece was mainly a tumor (infiltrating ductal carcinoma) with a small amount of normal tissues in the margins with an overall approximate dimension of 8 mm × 5 mm × 3 mm. An incision was made in the mid-plane (along the z-axis, which was the shorter dimension of the tissue) of the normal piece, and some amount of the normal tissue was removed from the central region making a small pouch. The tumor piece was then inserted into the pouch, and the incision was closed by moderate compression of the composite consisting of the normal tissue and the tumor along xyz-directions. The breast tissue slab was contained inside a transparent plastic box. One of the sides of the box could be moved to uniformly compress the tissue along the z-axis and hold it in position. The resulting specimen, a 70 mm × 55 mm × 33 mm slab, was treated as one entity in the subsequent imaging experiment. The position of the tumor within the slab was known since it was placed in the position as discussed earlier. One of the tests of the efficacy of this imaging approach was to see how well the known position is assessed.

A 200 μm optical fiber delivered a 784 nm, 300 mW continuous-wave beam from a diode laser for sample illumination. The beam was collimated to a 1 mm spot onto the entrance face (henceforth referred to as the "source plane")

of the slab sample. Multiple source illumination was realized in practice by step scanning the slab sample across the laser beam in an xy array of grid points using a computer-controlled translation stage. The xy array was 22×16 with a step size of 2.0 mm. The signal from the opposite face of the sample (henceforth referred to as the "detection plane") was collected by a camera lens and projected onto the sensing element of a cooled 16 b, 1024×1024 pixel CCD camera. Although the scanned area is 42 mm $\times$ 30 mm on the source plane, the imaged area of the detection plane was much larger, covering the entire 70 mm $\times$ 55 mm transverse area of the model breast. Each illuminated pixel of the CCD camera could be regarded as a detector. For illumination of every scanned point on the source plane, the CCD camera recorded the diffusely transmitted 2-D intensity pattern on the detection plane. Each image acquisition took 100 ms, and one stepping of the translational stage took 1 s. A total of 352 images were completed within 7 min. The OPTICA reconstruction and cross-section imaging is expected to be completed within 2 min once fully automated.

IV. Results

A typical 2-D raw image of transmitted light intensity distribution on the detector plane for illumination at a typical scanning position is shown in Fig. 1(c). The average of all the 22×16 images was used to obtain the optical property of the slab of breast tissue. The radial profile of the intensity of the transmitted light on the average image was fitted to that predicted by a diffusion model of light propagation inside a slab. The transport mean free path was assumed to be 1 mm, the value for a typical human breast tissue at 785 nm. The reduced scattering coefficient was then 1 mm^{-1}. From the decay of the radial profile of the intensity of the transmitted light, the average absorption coefficient of the entire model breast is found to be $\mu_a = 0.0039$ mm^{-1}. Each raw image is first cropped to retain the region within the window of 50.4 mm $\times$ 51.3 mm (out of a total 70 mm $\times$ 55 mm transverse area of the model breast) over which image reconstruction would be performed. The size of 1 pixel in the raw image is 187 μm $\times$ 187 μm. The raw images are binned by merging 5×5 pixels into one to enhance the SNR, resulting in a total of 352 images of 54×55 pixels each. All the binned images corresponding to illumination of the grid points in sequence were then stacked, and used as input for independent component analysis.

The independent light intensity distributions obtained by OPTICA is displayed in Fig. 2(a). The 3-D location of the targets were obtained from least squares fitting using (3). The fittings of the independent light intensities over lines passing through the maximum value and along the horizontal direction are displayed in Fig. 2(b). The tumor C is found at 14.8 mm from the detection plane and centered at (33.3, 21.5, 18.2) mm. In addition, two glandular sites were identified. The first glandular site A is found to be located at 2.5 mm from the detection plane and centered at (11.2, 22.4, 30.5) mm; the second glandular site B is at 14.6 mm from the detection plane and centered at (21.5, 37.3, 18.4) mm. Comparison of known and 3-D positions obtained from OPTICA for the cancer site and two glandular sites is given in Table I.

The cross-section image of the tumor obtained from a 2-D inverse Fourier transform of (5) is shown in Fig. 3 (left pane). The right pane of Fig. 3 displays the intensity profiles of the cross-section image along the x- and y-directions denoted by the white dashed lines. The FWHM values of the intensity profiles yield estimates of the lateral dimensions of the tumor to be 10.3 mm $\times$ 7.4 mm, while the known dimensions are 8 mm $\times$ 5 mm. Histological micrograph of the suspect site confirmed tumor. Similar back-projection cross-sectional images and histological micrographs were obtained (not shown here) for the glandular tissues as well and their transverse sizes were estimated from OPTICA. The existence, location, and size of the glandular tissues were not known *a priori*. The glandular structure A near surface is estimated to be 2.7 and 1.6 mm in size along the x- and y-directions from the cross-section image, respectively. The size of the glandular structure B at the midplane is 8.7 and 9.2 mm in size along the x- and y-directions, respectively.

Low regularization was used in generating the cross-section images in Fig. 3 to achieve maximal spatial resolution. The artifacts in the cross-section images can be suppressed with a higher regularization at a cost of lower spatial resolution. Since the target has been localized in the earlier stage of analysis, the target will not be confused with artifacts in the cross-section images and low regularization is beneficial here.

The investigated *ex vivo* breast sample contained minimal amount of blood, and hence, the reconstructed images are for the scattering property of the sample. The change of the reduced scattering coefficient μ_s' for the targets can further be estimated from the reconstructed independent components for the sites A, B and C. The value of $\delta\mu_s'$ is given by the ratio of the strength of the target and its volume. The sites A and B have lower scattering while the site C has enhanced scattering compared to the background (mainly adipose tissue). The values of $\delta\mu_s'$ are $\sim$0.2 and ~ -0.4 mm^{-1} for the tumor and glandular tissues, respectively. Subsequent pathological analysis confirmed the site C as infiltrating ductal carcinoma, and identified the other two structures as glandular breast tissues.

V. Discussion

The results of the experiments clearly demonstrate that OPTICA can locate the tumor inside the model breast with high accuracy. As can be seen from Table I, the lateral positions of the tumor agree within 0.5 mm, while the axial position agree within $\sim$1 mm of the known values. Similar high accuracy in the respective positions of the two pieces of glandular tissues is observed as well. The accuracy of the lateral positions does not depend significantly on the depth of the targets, while that of the axial position shows a weak dependence. For the target located close to the detection plane (glandular site A at a distance of 2.5 mm from the detection plane), the axial position is determined exactly, while for targets in the midplane that are much more challenging to locate, the accuracy is within 1 mm. Given

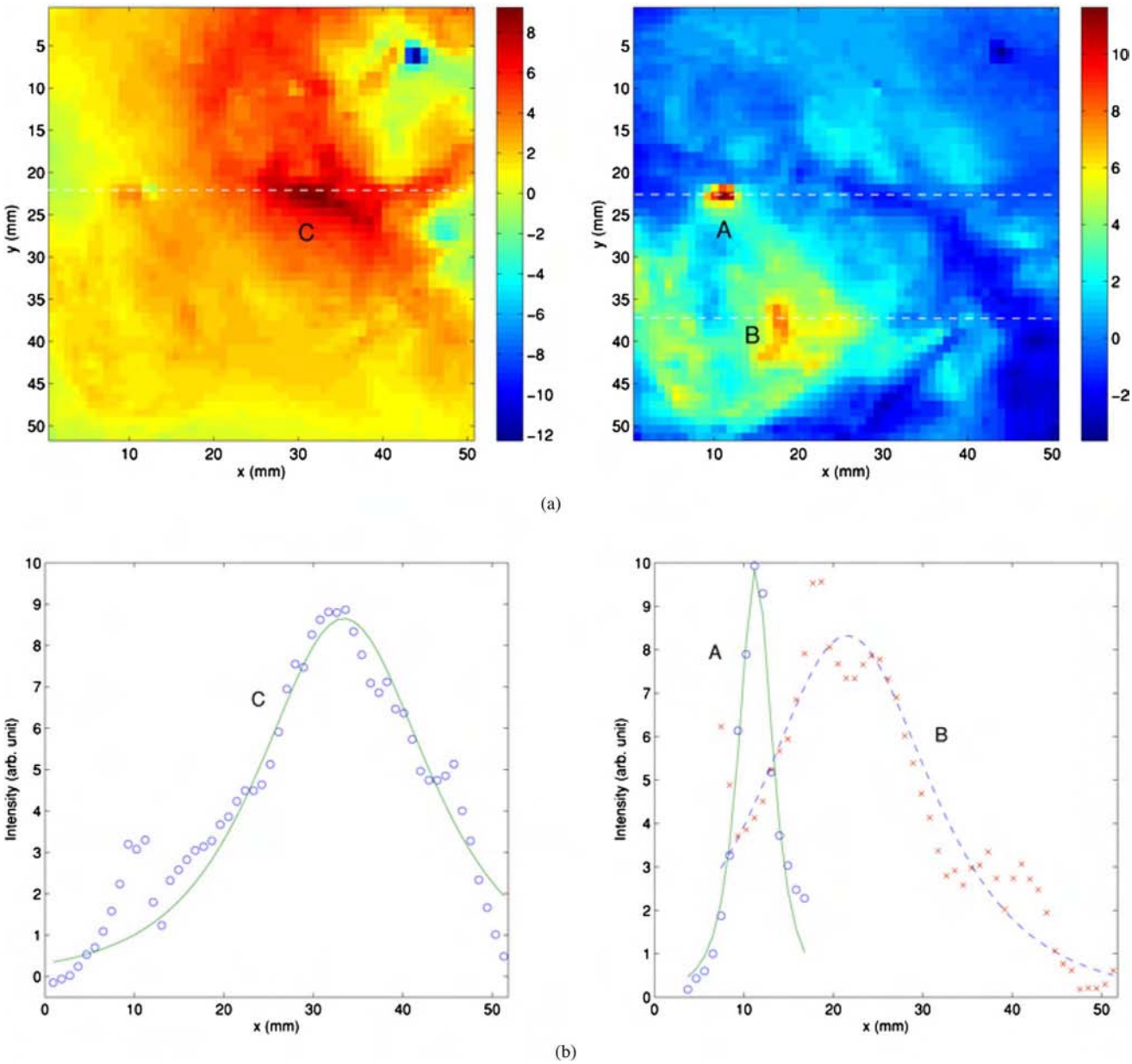

Fig. 2. (a) Independent intensity distribution on the detector plane ($z = 33$ mm) obtained by OPTICA for the tumor C (left pane) and the glandular structures A and B (right pane). (b) Corresponding bottom panes show the Green's function fits (solid lines) to the horizontal spatial profile (denoted by circles and crosses) through the center of the intensity distributions along the dashed lines.

TABLE I
COMPARISON OF KNOWN AND OPTICA ESTIMATED TARGET LOCATIONS

Target	Known Position (x, y, z) (mm)	OPTICA Estimated Position (x, y, z) (mm)
Cancer Site (C)	(33,21,16.9)	(33.3,21.5,18.2)
Glandular Site (A)	(11,22,30.5)	(11.2,22.4,30.5)
Glandular Site (B)	(21,37,17)	(21.5,37.3,18.4)

that light propagation is highly diffusive in breast tissues, this level of accuracy is quite significant.

The back-projection formalism estimates the FWHM values of the lateral dimension of the tumor to be 10.3 and 7.4 mm in size along the x- and y-directions, respectively, whereas the known dimension is 8 mm $\times$ 5 mm. This result is expected due to diffusion of light in the tissue, and is in line with the results that we obtained in our earlier OPTICA studies [26].

Another important finding was that OPTICA predicted different scattering properties for the adipose tissue (medium), the tumor, and the glandular tissues. The glandular tissues were found to be less scattering than the adipose tissues at the wavelength of interrogation, i.e., 784 nm. The tumor was found to be more scattering. These observations are consistent with the known literature values of scattering properties of different types of tissues [30].

The nature of the inhomogeneity (either absorptive or scattering or mixed) can be discerned by OPTICA with continuous-wave measurement when the SNR is high [20], [25]. When the SNR is not favorable, the recovered independent component

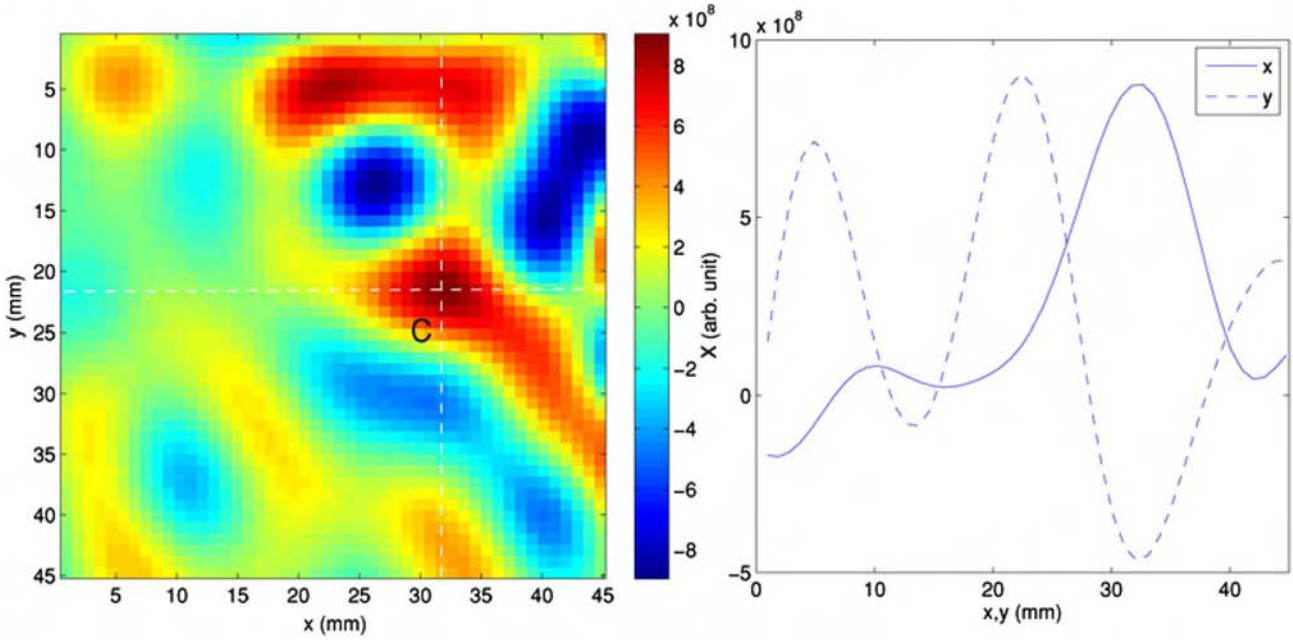

Fig. 3. Cross-section image of the tumor at the $z = 18.2$ mm plane formed by back-projection (left pane). Right pane: Spatial profiles of the cross-section image along the x- and y-directions shown by the white dashed lines (right pane). The FWHM of the cancer site is 10.3 and 7.4 mm along the x- and y-directions, respectively.

will be due to both absorption and scattering perturbations at the site of the inhomogeneity. The strength of the target will be proportional to $\delta\mu_a + \kappa^2\delta D = \delta\mu_a + (\mu_{a_0} - i\omega/c)\delta D/D_0$, which provides a way to discriminate between absorption and scattering if measurements of multiple modulation frequencies ω are available. The capability of OPTICA for separating absorption from scattering inhomogeneities can be significantly improved with a time-domain or frequency-domain measurement. Another enabling factor will be carrying out multispectral OPTICA studies for potential diagnostic information.

OPTICA can be used for fluorescent targets as well [26]. The same experimental arrangement may be used, except for the introduction of filters to block the excitation beam and to transmit the fluorescence light. What is even more interesting is that, a beam-splitter and two detectors combination with appropriate filters may be used to simultaneously pursue absorption/scattering OPTICA and fluorescence OPTICA studies of biological samples for obtaining coregistered information from dual probes.

OPTICA is suited to detect small objects. Given its ability to identify low-contrast small objects, the approach is expected to be especially useful for the detection of breast and prostate tumors at their early stages of growth.

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